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Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults

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Title: Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: a systematic review and meta-analysis

Authors:

Kathryn E. Lafond, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US; School of Health Sciences, University of Tampere, Tampere, Finland

Rachael M. Porter, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US

Melissa Whaley, US Centers for Disease Control and Prevention, Atlanta GA, US

Zhou Suizan, Influenza Division, US Centers for Disease Control and Prevention, Beijing, China

Zhang Ran, Influenza Division, US Centers for Disease Control and Prevention, Beijing, China

Mohammad Abdul Aleem, Program for Emerging Infections, Infectious Disease Division, icddr,b, Bangladesh

Binay Thapa, Royal Centre for Disease Control and Prevention, Thimphu, Bhutan

Borann Sar, Centers for Disease Control and Prevention, Phnom Penh, Cambodia

Viviana Sotomayor Proschle, Department of Epidemiology, Ministerio de Salud, Santiago, Chile

Zhibin Peng, Division of Infectious Diseases, Chinese Center for Disease Control and Prevention, Beijing, China

Luzhao Feng, School of Population Medicine & Public Health, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, China

Daouda Coulibaly, Institut National d'Hygiène Publique, Abidjan, Cote d'Ivoire

Edith Nkwembe, Institut National de Recherches Biomédicales, République Démocratique du Congo

Alfredo Olmedo, Ministerio de Salud, Quito, Ecuador

William Ampofo, Noguchi Memorial Institute for Medical Research, College of Health Sciences, University of Ghana, Accra, Ghana

Siddhartha Saha, Influenza Division, US Centers for Disease Control and Prevention, New Delhi, India

Mandeep Chadha, National Institute of Virology, Pune, India

Amalya Mangiri, US Centers for Disease Control and Prevention, Jakarta, Indonesia

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Vivi Setiawaty, National Institute of Health Research and Development, Jakarta, Indonesia

Sami Sheikh Ali, Ministry of Health, Amman, Jordan

Sandra S. Chaves, Influenza Division, US Centers for Disease Control and Prevention, Nairobi, Kenya

Dinara Otorbaeva, Department of State Sanitary Epidemiological Surveillance, Bishkek, Kyrgyzstan

Onechanh Keosavanh, National Center for Laboratory and Epidemiology, Vientiane, Lao People's Democratic Republic

Majd Saleh, Epidemiological Surveillance Program, Lebanese Ministry of Public Health, Beirut, Lebanon

Antonia Ho, MRC-University of Glasgow Centre for Virus Research, Glasgow, UK; Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi

Burmaa Alexander, National Centre for Communicable Disease, Ulaan Baatar, Mongolia

Hicham Oumzil, Virology Department, Institut National d'Hygiène, Rabat, Morocco; Faculty of Medicine, Microbiology RPU, Université Mohammed-V de Rabat, Rabat, Morocco

Kedar Prasad Baral, Patan Academy of Health Sciences, Lalitpur, Nepal

Q. Sue Huang, The WHO National Influenza Centre, Institute of Environmental Science and Research, New Zealand

Adedeji A. Adebayo, Nigeria Centre for Disease Control, Federal Ministry of Health, Abuja, Nigeria

Idris Al-Abaidani, Department of Communicable Diseases, Directorate General of Disease Surveillance and Control, Ministry of Health, Muscat, Oman

Marta von Horoch, Ministerio de Salud Publica y Bienestar Social, Asunción, Paraguay

Cheryl Cohen, National Institute for Communicable Diseases, Johannesburg, South Africa

Stefano Tempia, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US; School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Vida Mmbaga, Ministry of Health, Dar es Salaam, Tanzania

Malinee Chittaganpitch, National Institute of Health, Ministry of Public Health, Nonthaburi, Thailand

Mariana Casal, Arizona Department of Health Services, Phoenix, AZ US

Duc Anh Dang, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

Paula Couto, Pan American Health Organization, Washington, DC, US

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Harish Nair, Centre for Global Health Research, University of Edinburgh, Edinburgh, UK;
Public Health Foundation of India, New Delhi, India

Joseph Bresee, Influenza Division, US Centers for Disease Control and Prevention, Atlanta
GA, US

Sonja J. Olsen, Influenza Division, US Centers for Disease Control and Prevention, Atlanta
GA, US

Eduardo Azziz-Baumgartner, Influenza Division, US Centers for Disease Control and
Prevention, Atlanta GA, US

J. Pekka Nuorti, University of Tampere, Tampere, Finland

Marc-Alain Widdowson, Institute of Tropical Medicine, Antwerp, Belgium

Global Respiratory Hospitalizations –Influenza Proportion Positive (GRIPP) Working Group:

Meerjady Sabrina Flora, Institute of Epidemiology Disease Control and Research, Dhaka,
Bangladesh

Sonam Wangchuk, Royal Centre for Disease Control and Prevention, Thimphu, Bhutan

Rodrigo A. Fasce, Viral Diseases Subdepartment, Instituto de Salud Pública de Chile,
Santiago, Chile

María Fernanda Olivares, Ministerio de Salud, Santiago, Chile

Ying Qin, Division of Infectious Diseases, Chinese Center for Disease Control and
Prevention, Beijing, China

Jiandong Zheng, Division of Infectious Diseases, Chinese Center for Disease Control and
Prevention, Beijing, China

Herve Kadjo, Institut National d'Hygiène Publique, Abidjan, Cote d'Ivoire

Léonie Many Kitoto, Direction de la Lutte Contre les Maladies, Ministère de la Santé,
République Démocratique du Congo

Jenny Ojeda, Técnica de la Dirección Nacional de Vigilancia Epidemiológica

Julio Armero, Ministerio de Salud de El Salvador, San Salvador, El Salvador

Michael Adjabeng, Disease Surveillance Department, Ghana Health Service, Accra, Ghana

Ricardo Mena, Ministerio de Salud Publica y Asistencia Social, Guatemala City, Guatemala

Sanjay K. Rai, All India Institute of Medical Sciences, Delhi, India

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Shobha Broor, All India Institute of Medical Sciences, Delhi, India

Renu B. Lal, Influenza Program, Centers for Disease Control and Prevention, New Delhi, India

Catharina Praptiningsih, US Centers for Disease Control and Prevention, Jakarta, Indonesia

Ni Ketut Susilarini, National Institute of Health Research and Development, Jakarta, Indonesia

Krisna Nur, National Institute of Health Research and Development, Jakarta, Indonesia

Ghazi Sharkas, Ministry of Health, Amman, Jordan

Gideon Emukule, Centers for Disease Control and Prevention, Nairobi, Kenya

Kaliya Kasymbekova, World Health Organization, Bishkek, Kyrgyzstan

Nadine Haddad, Epidemiological Surveillance Program, Ministry of Public Health, Beirut, Lebanon

Pamela Mrad, World Health Organization, Beirut, Lebanon

Stephen Aston, Institute of Infection and Global Health, University of Liverpool, United Kingdom

Darmaa Badarch, National Centre for Communicable Disease, Ulaan Baatar, Mongolia

Shambhu Kumar Upadhyay, Patan Academy of Health Sciences, Lalitpur, Nepal

Tim Wood, Institute for Environmental Science and Research, National Centre for Biosecurity and Infectious Disease, Upper Hutt, New Zealand

Ibrahim Dalhatu, Centers for Disease Control and Prevention, Abuja, Nigeria

Maria Agueda Cabello, Ministerio de Salud Publica y Bienestar Social, Asunción, Paraguay

Veronica Tallo, Research Institute for Tropical Medicine, Manila, Philippines

Florette Treurnicht, National Institute for Communicable Diseases, Johannesburg, South Africa

Marietjie Venter, National Institute for Communicable Diseases, Johannesburg, South Africa;

Zoonoses Research Unity, Department Medical Virology, University of Pretoria, Pretoria, South Africa

Elibariki Mwakapeje, Ministry of Health, Dar es Salaam, Tanzania

Prabda Praphasiri, US Centers for Disease Control and Prevention, Nonthaburi, Thailand

Pongpun Sawatwong, US Centers for Disease Control and Prevention, Nonthaburi, Thailand

Chris Troeger, Institute for Health Metrics and Evaluation, Seattle, Washington, United States

Zimy Wansaula, US Centers for Disease Control and Prevention, Atlanta GA, US

Marian Fierro, Imperial County Public Health Department, El Centro, CA, US

Esmeralda Iniguez-Stevens, California Department of Public Health, San Diego, US

Thi Minh Thoa Nguyen, US Centers for Disease Control and Prevention, Hanoi, Vietnam

James Kile, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US

Danielle Iuliano, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US

Melissa Rolfes, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US

Joshua Mott, US Centers for Disease Control and Prevention, Nonthaburi, Thailand

Ann Moen, Influenza Division, US Centers for Disease Control and Prevention, Atlanta GA, US

***Corresponding authors:**

Kathryn E. Lafond

1600 Clifton Rd NE, Atlanta GA 30329, MS A-32

Email: gmi3@cdc.gov

Telephone: +1-404-639-3338

Marc-Alain Widdowson

Nationalestraat 155, 2000 Antwerp, Belgium

Email: mawiddowson@itg.be

Telephone: +32 32476666

Key Words *Influenza, human; Disease Burden; Hospitalization*

Abstract (413 words)

Background: Influenza illness burden is substantial, particularly among young children, older adults, and those with underlying conditions. Initiatives are underway to develop better global estimates for influenza-associated hospitalizations and deaths. Knowledge gaps remain regarding the role of influenza viruses in severe respiratory disease and hospitalizations among adults, particularly in lower-income settings.

Methods and Findings: We aggregated published data from a systematic review and unpublished data from surveillance platforms to generate global meta-analytic estimates for the proportion of acute respiratory hospitalizations associated with influenza viruses among adults. We searched nine online databases (Medline, Embase, CINAHL, Cochrane Library, Scopus, Global Health, LILACS, WHOLIS, and CNKI, 1/1/1996-12/31/2016) to identify observational studies of influenza-associated hospitalizations in adults, and assessed eligible manuscripts for bias using a simplified Newcastle-Ottawa scale for observational data. We applied meta-analytic proportions to global estimates of lower respiratory tract infections (LRIs) and hospitalizations from the Global Burden of Disease study in adults ≥ 20 years and by age groups (20–64 years and ≥ 65 years) to obtain the number of influenza-associated LRI episodes and hospitalizations for 2016.

Data from 63 sources showed that influenza was associated with 14.1% (95% confidence interval [CI]: 12.1%–16.5%) of acute respiratory hospitalizations among all adults, with no significant differences by age group. The 63 data sources represent published observational studies ($n=28$) and unpublished surveillance data ($n=35$), from all World Health Organization regions (Africa=8, Americas=11, Eastern Mediterranean=7, Europe=8, Southeast Asia=11, Western Pacific=18). Data quality for published data sources was predominantly moderate or high quality (75%, $n=56/75$).

We estimate 32,126,000 (95% CI: 20,484,000–46,129,000) influenza-associated LRI episodes and 5,678,000 (95% CI: 3,205,000–9,432,000) LRI hospitalizations occur each year among adults. While adults <65 years contribute most influenza-associated LRI hospitalizations and episodes (3,464,000 (95% CI: 1,885,000–5,978,000) LRI hospitalizations and 31,087,000 (95% CI: 19,987,000–44,444,000) LRI episodes), hospitalizations rates were highest in those ≥ 65 years (437/100,000 person-years (95% CI: 265–612/100,000 person-years)). For this analysis, published articles were limited in their inclusion of stratified testing data by year and age group. Lack of information regarding influenza vaccination of study population was also a limitation across both data sources.

Conclusions: In this meta-analysis, we estimated that influenza viruses are associated with over five million hospitalizations worldwide, per year. Inclusion of both published and unpublished findings

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allowed for increased power to generate stratified estimates, and improved representation from lower-income countries. Together, the available data demonstrate the importance of influenza viruses as a cause of severe disease and hospitalizations in younger and older adults worldwide.

Author Summary

Why was this study done?

- Every year, millions of people become infected with influenza viruses, which infect the airways and cause symptoms that include a fever, tiredness and weakness, general aches and pains, sore throat and cough.
- Most infected individuals recover quickly, but some develop more severe illness such as pneumonia, and may require hospitalization.
- Influenza vaccination can prevent infections and severe disease, but decisions on how to prioritize risk groups, particularly in limited-resource settings, require a robust evidence base, including global, regional, and local data.

What did the researchers do and find?

- We conducted a systematic review to identify published articles on influenza-associated respiratory disease in hospitalized adults.
- We then aggregated the data from these articles with data collected by hospital-based influenza surveillance, to calculate a pooled estimate of the proportion of adults hospitalized with respiratory disease who are positive for influenza.
- Through this approach, we estimated that influenza was associated with 14% of acute respiratory hospitalizations among adults worldwide.
- This equates to over five million influenza-associated hospitalizations per year, with highest rates among those 65 years and older.

What do these findings mean?

- Estimating the disease burden of influenza allows researchers and policymakers better understand its global impact across different target groups and allow comparisons with other causes of morbidity and mortality.
- As global populations age, the importance of vaccinating adults, particularly older adults, is likely to increase.

Introduction

Influenza viruses contribute substantially to respiratory disease worldwide, including severe lower respiratory tract illnesses, hospitalizations, and deaths. The highest rates of severe influenza-associated disease and hospitalization are typically reported among those at the extremes of age [1-4] and those with underlying health conditions [5]. To reduce the burden of influenza, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) recommends that countries initiating or expanding an influenza vaccination program prioritize pregnant women, children aged 6–59 months, adults ≥ 65 years, individuals with high-risk conditions, and healthcare workers [6]. During the COVID-19 pandemic, SAGE has also released interim recommendations prioritizing healthcare workers and older adults for influenza vaccination [7] .

Global influenza burden estimates generated to date include all-age estimates of hospitalizations and mortality, as well as age-specific estimates for paediatric hospitalizations [8-10]. Important gaps in knowledge remain about the burden of influenza-associated severe respiratory disease and hospitalizations in adults, particularly in lower-resource settings, because of the dearth of denominators for incidence calculations [11]. The objective of these analyses was to generate a global estimate of the annual number of respiratory hospitalizations and lower respiratory tract infections (LRIs) associated with influenza viruses among adults ≥ 20 years worldwide, utilizing published findings and unpublished laboratory-confirmed data from a global network of influenza surveillance partners.

Methods

Research objective and data sources

Our *a priori* research objective was to estimate the proportion of adult respiratory hospitalizations that tested positive for influenza (“proportion positive”) as a summary

statistic. We generated this estimate using two sources of data: a systematic review of the literature and unpublished respiratory inpatient surveillance data from a global working group of partners. We then applied the summary meta-analytic proportion positive to global estimates of adult LRI episodes and hospitalizations available for adults ≥ 20 years.

Systematic literature review: search strategy and selection criteria

We searched nine online databases (Medline, Embase, CINAHL, Cochrane Library, Scopus, Global Health, LILACS, WHOLIS, and CNKI) for articles published in any language from January 1, 1996 to December 31, 2016 to identify studies of influenza-associated hospitalizations in adults. Keywords included “influenza” and terms related to hospitalization (e.g., “hospital*,” “inpatient”) (Supplementary Table 1). Titles and abstracts of all articles identified were screened for inclusion in the analysis by a member of the review team (KL, RP, JK, MW, EAB, MAW) with support from native language speakers as needed. Chinese-language articles were screened by native Mandarin speakers (ZS and ZR). A random subset (25%) of articles were screened by a second reviewer for validation. An article was included for full-text review if at least one reviewer flagged it as potentially eligible. The inclusion criteria were: 1) an original study on human subjects; 2) laboratory testing for both influenza A and B viruses, with description of diagnostic method(s) used; 3) a minimum of 12 months’ continuous data; 4) a specified case definition or other clear criteria for systematic specimen collection and testing; 5) inclusion of hospitalized patients; 6) inclusion of the number of cases from whom clinical specimens were collected and the number found positive; and 7) a minimum of 50 adults >18 years of age (or an adult population, as described by authors) tested for influenza across the duration of the study.

We excluded studies that described nosocomial influenza infections or included data from calendar year 2009 (the initial wave of influenza A[H1N1]pdm09 virus circulation) in a manner that could not be separated from data from other years, since both influenza epidemiology and testing practices were atypical during this period. Although the influenza

A(H1N1)pdm09 pandemic period continued into 2010, this was often second-wave circulation and was not excluded from the analysis. For titles and abstracts meeting criteria, full-text articles were assessed independently by two members of the review team. Any discrepant decisions on full-text articles were first discussed between the two reviewers; those that could not be resolved (n=2) were adjudicated by a third reviewer (MAW).

From each eligible article, we abstracted the following data elements: 1) the total number of inpatients tested and total positive for influenza by age group and influenza type and subtype where available, 2) location and timeframe of data collection, 3) the case definition and diagnostic test(s) used, 4) the proportion of the study population with any underlying conditions (as defined by the paper), and 5) influenza vaccination coverage in the study population. We recorded whether the study population was a “special population,” defined as a selection of participants not representative of all inpatients (e.g., intensive care unit patients, or those with chronic obstructive pulmonary disease [COPD]). WHO region, World Bank income category (low, lower-middle, upper-middle, or high income), and pneumococcal conjugate vaccine (PCV) introduction status were assigned for each dataset, based on the country and start year of data collection [12, 13]. Quality of evidence for each published paper was evaluated on a simplified Newcastle-Ottawa scale, as described previously [8, 14]. Key variables (number tested and positive, laboratory method used, and quality score) were abstracted by two independent reviewers. We did not pre-register the protocol for this systematic review. A full list of eligible published articles with key abstracted data, and a PRISMA checklist for systematic reviews [15], are provided in Supplementary Materials (Supplementary Table 2, Supplementary Checklist 1).

GRIPP working group

To supplement data from published studies, we established a working group, Global Respiratory Hospitalizations – Influenza Proportion Positive (GRIPP), which compiled recent, typically unpublished data through 2016 from surveillance platforms conducting systematic

inpatient surveillance for influenza. Eligible surveillance platforms included those conducting systematic year-round inpatient testing using any acute respiratory case definition (e.g., severe acute respiratory infection [SARI], community-acquired pneumonia [CAP]) for at least 12 consecutive months and that tested at least 50 adult inpatients over the duration of the study. Minimum of 50 samples was selected to reduce within-study variance and remove undue influence of very small studies. We contacted seventy-three partners, of whom 37 (51%) had eligible adult data and agreed to participate in the GRIPP working group. We collected the following data in a standardized form: the number of persons tested and positive for influenza by calendar year and age group (18–64 years and ≥ 65 years), the total number of inpatient sites, case definition used, and any participant selection procedures. Patient comorbid conditions and influenza vaccination status were not frequently reported in partner surveillance platforms, and were not collected on the standardized form. If surveillance data were also represented in a manuscript identified through systematic review, the working group dataset was used, and the published article was excluded as a duplicate source. Working group data were not scored for quality in the same manner as published articles, but were reviewed for completeness and internal consistency of primary results. Influenza virus detections were reported by type and A subtypes where available; however, as influenza B virus lineage testing was rarely conducted during the study period, it was not included in the current analyses.

Statistical analysis

We explored all data from both published and unpublished sources in the univariate analysis of median proportion positive by categorical variables (such as diagnostic test used, case definition, WHO region, and country income classification). We tested for differences in frequencies across groups using chi-square. Since the proportion of respiratory samples testing positive for influenza was not normally distributed, we estimated median values and interquartile ranges (IQRs), and used Kruskal-Wallis non-parametric ANOVA to compare the

summary proportion positive per dataset/study across groups. We used a p-value of <0.05 as our threshold for significance.

To minimize variability observed among data sources in the univariate analysis, we limited the meta-analysis to data derived from gold-standard RT-PCR diagnostic testing and excluded all studies of special populations to estimate the proportion of adult respiratory hospitalizations positive for influenza. To derive meta-analytic estimates of proportion positive, we used a log-binomial mixed model with a random effect for data source that allowed for inclusion of multiple years of data within a single data source [8]. I^2 was calculated as variance across datasets as a percentage of total variance in each model. We generated overall, age-stratified (20–64 and ≥ 65 years), and influenza A and B virus-specific proportion positive estimates. Virus type-specific models were restricted to datasets with at least one type-specific positive sample.

Overall and age-specific meta-analytic estimates of proportion positive were multiplied by LRI hospitalization and LRI episode estimates for adults ≥ 20 years, which were from the Global Burden of Disease (GBD) 2017 study [10], obtained for calendar year 2016 for this analysis. The GBD study models incidence of lower respiratory infection episodes and hospitalizations at a global and regional level, by age group, using a Bayesian meta-regression tool. Confidence intervals for our multiplied estimates of number of influenza-associated events were created through a Monte Carlo resampling process that assumed normal distribution for denominators and binomial distributions for the modelled proportion positive estimates, using 95% confidence intervals as lower and upper bounds, with 5,000 iterations. We calculated rates by dividing the above estimates by 2016 global population [16]. Post-hoc sensitivity analyses were conducted to explore patterns in heterogeneity (I^2) of the pooled proportion positive and percent change in the estimated number of hospitalizations by stratifying for key covariates. All statistical analyses were conducted in R version 3.5.2, with package “lme4” for mixed models [17, 18].

Ethical approval was not required for this study.

Results

The systematic literature search identified 18,945 unique articles published between January 1996 and December 2016, describing data collected from 1982 through 2016. An additional 21 articles were identified outside the search through consultation with subject-matter experts and review of references. Of these 18,966 articles, we reviewed 1,158 full-text articles; 75 met the inclusion criteria and were abstracted for the descriptive analysis (Figure 1). Combining these with the 37 GRIPP working group surveillance datasets, we included 112 unique influenza data sources from 55 countries across all six WHO regions. Compared with published articles, surveillance datasets were more likely to use RT-PCR as the primary method of diagnosis ($n=35/37$, 95% vs. $n=38/75$, 51%, $p<0.001$) and more likely to use SARI a WHO-recommended case definition for severe influenza disease [19] as case definition (78% vs. 8%, $p<0.001$). Surveillance datasets were also more commonly from low- and lower-middle income countries, compared with published articles (67% vs. 14%, $p<0.001$). Approximately 57% of published articles presented <2 years of data, versus 8% of surveillance datasets ($p<0.001$). Special populations were the specific focus of 27% ($n=20/75$) of published articles, and none of the surveillance datasets (Table 1). Frequency of comorbid conditions was reported for 47 (63%) of 75 published articles, with a range of 25% to 100% of patients having one or more conditions. Influenza vaccination status of patients was only reported by five articles; vaccine coverage ranged between 7% and 48% .

Among all data sources ($n=112$), the median percent of respiratory samples that were influenza positive among adult patients <65 years was similar to that among those ≥ 65 years (15%, IQR 9–21% vs. 13%, IQR 8–17%, respectively; $p=0.280$). The median percent positive was higher among surveillance data compared to published articles (15%, IQR 10–20%, vs. 10%, IQR 6–17%, $p=0.011$). The median percent positive was higher among middle-income countries than low- or high-income countries ($p=0.035$). Case definition was

also influential, with higher values among studies using SARI or LRI compared to those using acute respiratory infection (ARI) or pneumonia. The percent of patients positive for influenza was not associated with diagnostic test used (Supplementary Table 3). When we restricted the data to the subset of studies that were included in the meta-analysis—i.e., those using RT-PCR data (excluding special populations), shown in Table 2—the median proportion positive differed only by case definition as indicated by post hoc non-parametric pairwise testing (Dunn's test with Bonferroni correction) which identified a significant difference between pneumonia-based estimates and SARI-based estimates ($p=0.0047$).

Data by year and influenza A virus subtype were primarily available from post-2009 pandemic surveillance conducted by the GRIPP working group (Figure 2). While different virus types and subtypes predominated from year to year within individual datasets, the yearly median percent positive across datasets showed influenza A viruses were detected approximately three times more frequently than influenza B viruses, with generally equal frequency of influenza A(H1N1) and influenza A(H3N2) viruses in any given year. An increasing trend was seen in influenza A (overall and both subtypes), but not influenza B during this time.

The primary meta-analysis model ($n=63$ datasets) found influenza to be associated with 14.1% (95% CI: 12.1–16.5%) of acute respiratory hospitalizations (all adults). Influenza A viruses were associated with an estimated 10.6% (95% CI: 8.9–12.5%) of these episodes and influenza B viruses with 3.5% (95% CI: 2.8–4.3%). Applying the overall percent influenza-positive to estimates of hospitalized and total LRI episodes resulted in a total of 5,678,000 (95% CI: 3,205,000–9,432,000) influenza-associated LRI hospitalizations and 32,126,000 (95% CI: 20,484,000–46,129,000) influenza-associated LRI episodes in persons ≥ 20 years globally. Using age-specific proportion positive estimates, this equated to 3,464,000 (95% CI: 1,885,000–5,978,000) influenza-associated hospitalizations among adults 20–64 years and 2,831,000 (95% CI: 1,716,000–3,969,000) influenza-associated hospitalizations among adults ≥ 65 years (Table 3). From these estimates, we calculated a

rate of 80 (95% CI: 44–139) hospitalizations/100,000 population among adults <65 years and 437 (95% CI: 265–612) hospitalizations/100,000 population among older adults. By virus type, we estimated 4,264,000 (95% CI: 2,185,000–7,353,000) influenza A–associated and 1,408,000 (95% CI: 322,000–3,034,000) influenza B–associated hospitalizations each year, as well as 24,126,000 (95% CI: 13,880,000–36,677,000) influenza A–associated and 7,966,000 (95% CI: 1,650,000–15,426,000) influenza B–associated LRI episodes. Regional estimates are presented in Supplementary Table 4. Additional model data and sensitivity analyses are presented in Supplementary Table 5. A forest plot of findings by dataset is presented in Supplementary Figure 1.

Discussion

We estimated that seasonal influenza viruses were associated with 14% of acute lower respiratory disease among hospitalized adults. In 2016, this equated to 5.7 million influenza-associated LRI hospitalizations and 32.1 million LRI episodes globally. The majority of hospitalizations and episodes occurred among younger adults, although influenza-associated hospitalization rates were five times higher among older adults. Three-quarters of episodes (24 million) were associated with influenza A viruses of any subtype, and one-quarter (8 million) were associated with influenza B viruses.

These estimates are consistent with, or slightly higher than, existing global estimates of influenza morbidity and mortality. Our model adds to the existing knowledge by providing an estimate focused specifically on adult populations, adding a large amount of additional influenza-specific data from unpublished surveillance data over several years from a diverse range of countries where publications are often not available, and allowing for validation and triangulation across models. The 2017 GBD Study found that influenza was associated with 9.5 million LRI hospitalizations worldwide among all age groups, with a majority of these occurring among children 19 years and younger. This estimate was based on an attributable fraction estimate for all ages of 8.5%, derived from a systematic literature review of

published studies, but was lower than our estimate for adults (14%), as well as our previous estimate for older children (16%) [8, 10]. Their approach might underestimate the attributable fraction of influenza among adults because of the inclusion of paediatric patients, who are less likely to test positive for influenza. The attributable fraction used in the GBD analysis also included data derived from less-sensitive diagnostic assays (i.e., ELISA) in addition to RT-PCR–diagnosed influenza [20].

By comparing our estimated LRI episodes and hospitalizations to published estimates of global influenza mortality, we are also able to validate our estimated outcomes. Recent estimates suggest that influenza is associated with 291,243–645,832 deaths per year [9]. Assuming the majority of deaths occur among adults, and using the upper bound of their estimate, this would translate to 11% of influenza-associated hospitalizations and 2% of influenza-associated LRI episodes, which are consistent with parameters from the US burden of disease pyramid for influenza [21].

This analysis is subject to several limitations. Our model summarizes the magnitude of influenza-associated hospitalizations across many years to determine the proportion that are influenza-associated in any one year. However, the proportion of respiratory disease caused by influenza in a given setting or year can be affected by a wide range of factors, such as specimen type, case definition, influenza and pneumococcal vaccine use, characteristics of predominating influenza viruses, and trends in circulation of other pathogens. We attempted to understand and control for these factors in the current analysis through our inclusion criteria (sampling process used, year-round diagnostic testing) and stratified analysis (by case definition and other factors). The proportion of patients with respiratory disease who are hospitalized is also affected by many factors, such as access to care and health-seeking behaviour; diagnostic, admission, and referral practices; age; and underlying health status, which likely differ by study site. An additional challenge for this analysis was the relatively limited amount or lack of stratified data (by year, age group, virus subtype, presence of underlying conditions, region, vaccination history) from both published and unpublished data

sources to make for robust stratified analyses (e.g. by region). Further, laboratory diagnosis of influenza in a case of adult LRTI may not mean that influenza infection was the cause of hospitalization, as we did not account for other pathogens or underlying factors. Finally, our estimates for LRI episodes are generated with a proportion influenza-positive derived from hospitalized illnesses. Total LRI episodes include illnesses that may or may not be hospitalized; in lower-income settings access to hospital services can be limited, therefore individuals with illnesses who do not seek care are likely to share similar characteristics with those who do. The proportion associated with influenza may be similar between those who are and are not hospitalized in these settings. Moreover, previous global analyses [10] indicate that non-severe LRI is often more likely to be influenza-positive than severe LRI, and thus applying the hospitalized percent positive to potentially milder non-hospitalized LRI cases suggests that we may have underestimated the true burden of total influenza-associated LRI episodes worldwide.

Conclusions

The burden of severe influenza-associated disease and hospitalizations among adults worldwide is substantial. While older adults, young children, pregnant women, and those with chronic illness are already recommended as target groups for vaccination by WHO, influenza vaccine uptake is low globally, and the standard-dose, inactivated influenza vaccines predominantly used in these settings may have a lower effectiveness in key populations such as older adults, compared to younger adult populations [22]. Efforts to improve influenza vaccines (e.g., via high-dose or adjuvanted formulations) and expand vaccination programs in low- and middle-income countries could lead to more routine vaccination and thus increase protection against severe influenza disease [23-25]; however, these initiatives require substantial investment of time and resources.

Given these challenges, and variations in incidence within and between nations and regions, high-quality surveillance data will continue to play a pivotal role in informing influenza

prevention and control measures, particularly in elucidating influenza virus infection's role as a cause of severe respiratory disease and hospitalizations among adults. Moreover, with the emergence of SARS-CoV-2 this study emphasises the critical importance of unbiased surveillance using standard case definitions in a wide range of settings in understanding global and regional impact of respiratory diseases.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1. Description of published studies and Global Respiratory Hospitalizations –Influenza Proportion Positive (GRIPP) surveillance datasets summarizing influenza-associated respiratory hospitalizations among adults, 1996–2016

	Published studies, n=75		Surveillance datasets, n=37		p-value
	n	%	n	%	
Age group					
Adults <65 years*	14	19%	36	97%	<0.001
Adults ≥65 years	32	43%	16	43%	0.95
All adults	75	100%	37	100%	
Study duration in years					<0.001
1 to 2	43	57%	3	8%	
3 to 4	31	41%	14	38%	
5+	1	1%	20	54%	
Study year (Range)	(1982–2016)		(2005–2016)		
Timeframe					<0.001
Pre-2009 data only	45	60%	0	0%	
Post-2009 data	30	40%	31	84%	
Both pre- and post-2009 data	0	0%	6	16%	
Total number of specimens tested					<0.001
50–99	12	16%	1	3%	
100–499	48	64%	7	19%	
500–999	9	12%	5	14%	
1000+	6	8%	24	65%	
Diagnostic Test					<0.001
RT-PCR only	23	31%	17	46%	
Immunofluorescence only	12	16%	0	0%	
Serological assay only	13	17%	0	0%	
Multiple tests, including RT-PCR	18	24%	20	54%	
Multiple tests, excluding RT-PCR	6	8%	0	0%	
Other [†]	3	4%	0	0%	
Case definition					<0.001
Acute respiratory infection (ARI)	6	8%	1	3%	
Lower respiratory infection (LRI)	3	4%	5	14%	
Pneumonia	32	43%	0	0%	
Severe acute respiratory infection (SARI)	6	8%	29	78%	
Other [‡]	28	37%	2	5%	
Special population[¶]					<0.001
Yes	20	27%	0	0%	
No	55	73%	37	100%	
World Health Organization region					<0.001
Africa	1	1%	8	22%	
Americas	11	15%	7	19%	
Eastern Mediterranean	4	5%	4	11%	
Europe	22	29%	1	3%	
Southeast Asia	5	7%	9	24%	
Western Pacific	32	43%	8	22%	
World Bank income level					<0.001

Global Adult Hospitalizations for Influenza

Low	1	1%	9	24%
Lower-middle	10	13%	16	43%
Upper-middle	24	32%	7	19%
High	40	53%	5	14%
Quality score (published studies only)[§]				
0	2	3%		
1	17	23%		
2	36	48%		
3	20	27%		
Included in meta-analysis				<0.001
Yes	28	37%	35	95%
No	47	63%	2	5%

*Gaps in age-specific estimates due to lack of outcome data stratified by age group.

† Includes rapid immunochromatographic assay (n=2), virus culture (n=1)

‡ Includes acute exacerbation of chronic obstructive pulmonary disease (COPD) (n=14), respiratory hospitalization (acute or non-acute) (n=10), acute exacerbation of asthma (n=3), acute febrile illness (n=2), intubation among intensive care unit (ICU) patients (n=1), acute respiratory distress syndrome (ARDS) (n=1), ICD-codes consistent with influenza (n=1), and acute coronary syndrome with recent influenza-like illness (n=1).

¶ Includes studies of populations with COPD (n=10), hospitalised in the ICU only (n=3), immunocompromising conditions (n=1), asthma (n=1), heart disease (n=1), or in the military (n=1).

§ Quality of included articles was assessed using a simplified Newcastle-Ottawa Scale [9, 15]. Possible quality score from 0 (lowest) to 3 (highest).

Table 2. Median number of specimens tested and percent positive for influenza, by age group, study design, and population among studies included in the meta-analysis

	Number of data sources (n=63)	Median total number specimens tested	Interquartile Range (IQR)		Median percent positive	IQR		p value
All adults	63	510	225	2,092	13%	8%	19%	
Age group*								
18-64 years	41	867	341	2,759	16%	11%	21%	0.17
65+ years	38	198	81	890	14%	9%	17%	
Data source								
Surveillance	35	1,376	542	3,775	15%	10%	20%	0.089
Published	28	225	120	349	10%	7%	18%	
Timeframe								
Pre-2009 data	14	191	124	242	9%	8%	12%	0.097
Post-2009 data	45	987	328	2,818	15%	9%	20%	
Pre- & post-2009 data	4	5,948	2,581	9,527	10%	10%	13%	
Case definition								
Acute respiratory infection (ARI)	6	254	126	279	10%	4%	13%	0.0064
Lower respiratory infection (LRI)	7	1,158	513	6,140	13%	11%	15%	
Pneumonia	12	182	120	258	8%	6%	10%	
Severe acute respiratory infection (SARI)	33	1,720	426	3,222	17%	11%	21%	
Other†	5	510	256	582	10%	9%	17%	
World Health Organization region								
Africa	8	1,490	491	1,797	9%	6%	11%	0.071
Americas	11	328	210	4,081	13%	7%	18%	
Eastern Mediterranean	7	987	361	2,743	20%	20%	22%	
Europe	8	191	134	262	9%	7%	11%	
Southeast Asia	11	1,130	456	2,573	14%	11%	18%	
Western Pacific	18	485	259	2,458	15%	10%	19%	
World Bank income level								
Low	9	1,253	565	1,766	12%	11%	14%	0.14
Lower-middle	20	785	312	2,952	16%	10%	21%	
Upper-middle	16	467	237	1,737	15%	9%	21%	
High	18	294	188	1,822	10%	7%	15%	

*Gaps in age-specific estimates due to lack of outcome data stratified by age group.

† Includes respiratory hospitalization (acute or non-acute) (n=4), ICD codes consistent with influenza (n=1).

Table 3. Global estimates of influenza-associated lower respiratory tract infection (LRI) episodes and hospitalizations, by age group

	All-cause estimate * (95% CI) [thousands]	Pooled percent influenza positive **(95% CI)	Number of datasets	Influenza-associated events (95% CI) [thousands]	Rate per 100 000 population (95% CI)
<i>All adults—any influenza</i>					
Hospitalized LRI episodes	40,226 (25,810–59,569)	14.1% (12.1%–16.5%)	63	5,678 (3,205–9,432)	115 (65–190)
LRI episodes	227,603 (190,403–268,571)			32,126 (20,484 – 46,129)	649 (414–931)
<i>All adults–influenza A</i>					
Hospitalized LRI episodes	40,226 (25,810–59,569)	10.6% (8.9%–12.5%)	51	4,264 (2,185–7,353)	86 (44–148)
LRI episodes	227,603 (190,403–268,571)			24,126 (13,880– 36,677)	487 (280–740)
<i>All adults–influenza B</i>					
Hospitalized LRI episodes	40,226 (25,810–59,569)	3.5% (2.8%–4.3%)	46	1,408 (322–3,034)	28 (7–61)
LRI episodes	227,603 (190,403–268,571)			7,966 (1,650–15,426)	161 (33–311)
<i>Adults 20–64 years—any influenza</i>					
Hospitalized LRI episodes	20,939 (12,894–32,704)	16.5% (13.7%–19.8%)	41	3,464 (1,885–5,978)	80 (44–139)
LRI episodes	187,893 (155,794–223,148)			31,087 (19,987– 44,444)	722 (464–1,032)
<i>Adults ≥65 years—any influenza</i>					
Hospitalized LRI episodes	19,287 (12,916–26,866)	14.7% (12.7%–16.8%)	38	2,831 (1,716–3,969)	437 (265–612)
LRI episodes	39,709 (34,609–45,423)			5,830 (4,927–6,740)	899 (760–1,040)

*All-cause estimates are derived from Global Burden of Disease project, adapted for 2016, among individuals 20 years and older.

**Percent positive and number of datasets from meta-analysis

Figure 1. Flow diagram for systematic review process (separate file)

Figure 2. Median proportion of adult respiratory samples testing positive for influenza virus by year and virus type/subtype, 2010 to 2016 (separate file)

Supplementary Material

S1 Table. Literature search methodology and results, by database

S2 Table. Summary of published articles included in the analyses, with reference list

S3 Table. Median number of specimens tested and percent positive for influenza, by age group, study design, and population among all data sources

S4 Table. Regional estimates of influenza-associated lower respiratory tract infection (LRI) episodes and hospitalizations, by age group

S5 Table. Sensitivity analyses

S1 Figure. Forest plot of individual study estimates included in meta-analysis (all adults)

S1 Checklist. PRISMA Checklist

S1 Data. CSV-formatted analysis dataset